A Synthetic Pathway to Obtain Heterocyclic Derivatives Containing Isoxazole and Tetrazole Rings Joined by a Carbohydrate Tether

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A synthetic route to obtain compounds with two different heterocycles, such as isoxazole and tetrazole rings, in the same molecule from carbohydrate derivatives using 1,3-dipolar cycloaddition is described. The new compounds involved in this synthesis are physically and spectroscopically characterized.

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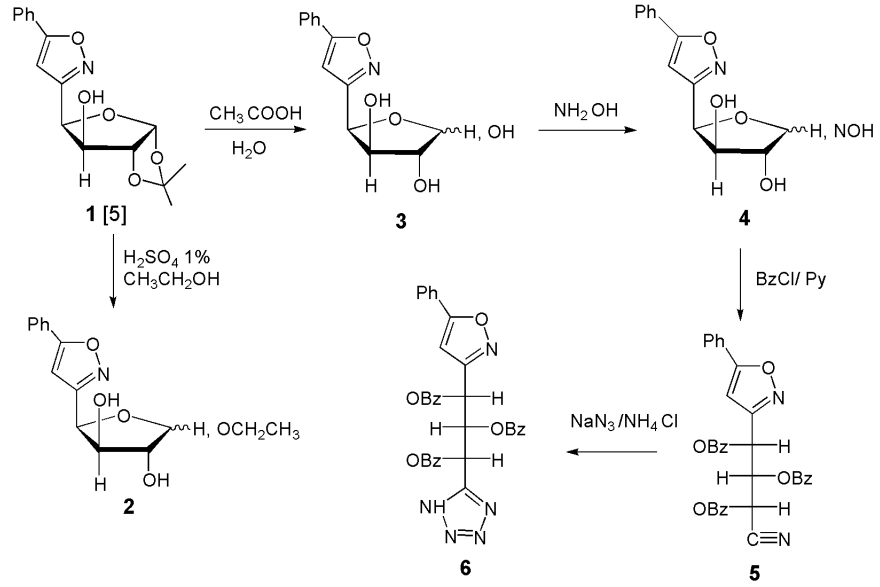
The synthesis of heterocyclic rings containing nitrogen atoms became of great importance in medicinal chemistry. Some heterocyclic rings such as the 2-isoxazole derivatives are used as membrane muscle relaxants [1] and for the treatment of hypercholesteremia, arteriosclerosis, and hyperlipimia [2]. The tetrazole rings have been used as glycosidase inhibitors [3], antihypertensives, antiallergics and antibiotics [4]. Both, tetrazole and 2-isoxazole rings, can be obtained by an 1,3-dipolar cycloaddition reaction. Our purpose was to synthesize a di-heterocyclic compound from glucose, which contained the rings previously named.

The following synthetic scheme was designed:

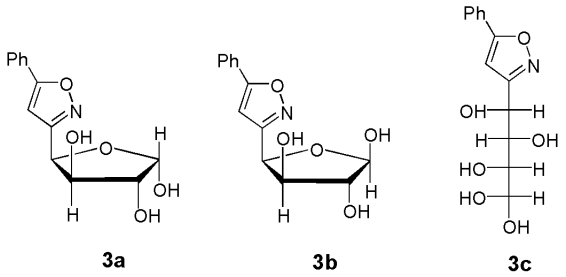


The 3-(1,2-*O*-isopropylidene-α-D-xylofuranos-4-yl)-5-phenyl isoxazole (**1**) was synthesized as we previously described [5].

In order to obtain a second heterocyclic moiety, we deprotected the isopropylidene group. When we used sulphuric acid (1%) in ethanol we isolated a product which was characterizated as 3-(ethyl D-xylofuranosid-4-yl)-5-phenylisoxazole (**2**).

To avoid the formation of compound **2**, we changed the hydrolysis conditions, by using acetic acid in water (10:90), and 3-(D-xylofuranos-4-yl)-5-phenylisoxazole (**3**) was finally obtained, with moderated yield. The spectroscopic analysis showed the signals corresponding to both anomers (α and β), together with other signals corresponding to the *gem*-diol form (Figure 2). Serianni and colleagues [6] described that a significant proportion of this species existed in an erytrose and treose solution.

When less water was used, such as acetic acid:water (50:50), only anomeric mixture signals were observed. A total assignment of the different signals corresponding to each species in the equilibrium mixture was obtained using two dimensional spectra (HETCOR) and spectroscopic data for related compounds [7]. The ^{1}H nmr spectra were performed at 500 MHz and allowed a first order analysis. In Table 1 and 2 we show the chemical shifts and coupling constants respectively, for the different equilibrium species of compound **3**. All ^{13}C nmr spectra were recorded on the same apparatus at 125 MHz, and the assignment of signals is shown in Table 3.



3a **3b** **3c**

Table 1

^{1}H nmr chemical shifts (δ) for equilibrium species **a - c** of compound **3**, measured at 500 MHz in methanol-d_4

Species	H-4	H-1'	H-2'	H-3'	H-4'
3a	6.78	5.61	4.14	4.37	5.37
3b	6.91	5.29	4.17	4.25	5.35
3c	6.81	4.63	4.01	4.07	5.00

[a] Aromatic protons: 7.28 -7.85 ppm.

Table 2

Measured coupling constants (Hz) for equilibrium species **a - c** of compound **3**

Species	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$
3a	4.0	3.6	4.4
3b	< 1	1.6	4.5
3c	6.2	2.3	6.6

Table 3

^{13}C nmr Chemical shifts for equilibrium species **a - c** for compound **3**, measured at 125 MHz in methanol-d_4

Species	C-3	C-4	C-5	C-1'	C-2'	C-3'	C-4'
3a	164.4	101.1	171.1	98.5	77.8	78.5	75.6
3b	164.8	101.8	170.6	104.7	82.0	78.2	78.6
3c	164.2	99.7	170.2	99.2	73.8	73.9	69.2

[a] Aromatic carbons 126.3 -130.9 ppm.

The treatment of **3** with hydroxylamine in methanol gave compound **4** in quantitative yield. The oxime derivative was isolated as cyclic forms, therefore the duplication of the ^{13}C and ^{1}H nmr signals was observed.

The nitrile **5**, was prepared for dehydratation and benzoylation of the oxime **4**, using benzoyl chloride in pyridine. An unequivocal characterization of compound **5**, was made using ^{1}H and ^{13}C nmr and two dimensional heteronuclear spectra. The ^{1}H nmr spectrum showed coupling constants of $J_{2',3'}$ = 5.7 Hz and $J_{3',4'}$ = 5.1 Hz, between the H-2'-H-3' and H-3'-H-4' respectively. These values indicated the deviations from the extended, planar, zig zag conformations, due to 1,3 interactions between the benzoyl groups on the C-2' and C-4'. Similar observations were previously reported [8] for other benzoylated derivatives. The ^{13}C nmr spectrum showed in addition to the signals corresponding to the isoxazole ring, carbonyl groups and aromatic carbons, a signal at 114.1 ppm was assigned to the nitrile carbon and three signals at 60.2, 66.5 and 70.6 ppm was assigned the aliphatic carbons. We assigned the signal at 60.2 ppm to the vicinal carbon of nitrile [9]; the adjudication of the other two signals were made by using coupling constants of the ^{1}H nmr spectrum and two dimensional heteronuclear spectrum as we describe in the Experimental. In the electron impact mass spectrum of compound **5** the molecular ion (m/z 572, 0.6%) and the characteristic fragments ions of perbenzoylated compounds are observed (see Experimental).

Treatment of compound **5** with ammonium azide, generated *in situ* from sodium azide and ammonium chloride, yielded compound **6** in moderate amount. The ^{1}H nmr spectrum showed coupling constants of $J_{1',2'}$ = 5.7 Hz and $J_{2',3'}$ = 5.1 Hz and therefore we infer that the preferential conformation in solution is similar to that of compound **5**. The ^{13}C nmr spectrum showed signals corresponding to isoxazole, carbonyl, aromatic, the tetrazole carbon (155.9 ppm) and corresponding to the three hydrocarbonated chain signals. The signal at 66.0 ppm is assigned to the carbon adjacent to the tetrazol ring. The total assignment was made using two dimensional nmr techniques. The data are shown in the Experimental section.

This synthetic pathway allowed us to obtain a di-heterocyclic compound linked through the hydrocarbonated chain, from glucose. These rings were chosen because it may be possible to transform them into compounds with potential biological activities. For example: the tetrazole ring can be transformed into 2,5-disubstituted-1,3,4-oxadiazol [10]; the cleavage of isoxazole ring brings on polyfonctionalizated molecules [11]; the nitrile can be use as a precursor for the synthesis of 1,2,4-oxadiazol [12]. These examples show the great and attractive possibilities of this synthetic way.

EXPERIMENTAL

General Methods.

The melting points were measured on a Thomas Hoover melting point apparatus and are uncorrected, and the optical rotation, $[\alpha]_D$, measurements were made using a 343 Perkin Elmer Polarimeter. Compound **1** was synthesized as we described in literature [5]. The ^{1}H nmr spectra were recorded at 200 MHz or at 500 MHz and the solvent used is reported in each case, using tetramethylsilane as internal standard. The ^{13}C nmr were recorded at 50 MHz or 125 MHz. Mass spectra were made with a Shimadzu QP-5000 by electron impact ionization. Mass spectra with fast atom bombardment ionization was performed with a ZAB-SEQ 4F using orthonitrobenzyl alcohol matrix.

3-(Ethyl D-xylofuranosid-4-yl)-5-phenylisoxazole (**2**).

Compound **1** (0.31 g, 1 mmol) was treated with sulphuric acid 1% in ethanol. The mixture was heated at 60 °C during 9 or 10

hours monitoring the reaction using tlc (silicagel G, toluene:ethyl acetate 1:1), until the starting material is disappeared. The reaction product was neutralized and evaporated at reduced pressure. The resulting syrup was purified by chromatography column (silicagel G, mixtures of cyclohexane:acetone), pure compound **2** was obtained as a syrup (0.12 g, 0.1 mmol, 42 % yield); ^{1}H nmr (deuterioacetone) for α-anomer: δ 7.88-7.49 (5H, m, aromatic protons), 6.60 (s, H-4), 5.04 (d, $J_{4',3'}$= 5.3 Hz, H-4'), 5.01 (d, $J_{1',2'}$= 4.3 Hz, H-1'), 4.13 (m, H-2'), 3.99 (m, H-3') and for β-anomer: δ 7.88 - 7.49 (5H, m, aromatic protons), 6.59 (s, H-4), 5.81 (s, H-1'), 4.13 (m, H-2'), 5.15 (d, $J_{4',3'}$= 4.4 Hz, H-4'), 3.95 (m, H-3'); ^{13}C nmr (deuterioacetone) for α–anomer: δ 169.6 (C-5),163.9 (C-3), 130.8, 129.9, 128.5, 126.3 (aromatic carbons), 102.8 (C-1'), 101.5 (C-4), 78.6 (C-2'), 78.3 (C-3'), 75.4 (C-4'), 64.8 (CH_2), 15.4 (CH_3) and for β-anomer: δ 169.6 (C-5),164.2 (C-3), 130.8, 129.9, 128.5, 126.3 (aromatic carbons), 109.5 (C-1'), 101.4 (C-4), 81.5 (C-2'), 78.7 (C-3'), 78.4 (C-4'), 68.2 (CH_2), 15.4 (CH_3); ms: m/z 292 (M + H^+), 273 ($M^{+\bullet}$ - H_2O), 246 ($M^{+\bullet}$ - $CH_3CH_2O^\bullet$), 228 ($M^{+\bullet}$ - H_2O - $CH_3CH_2O^\bullet$), 216 ($M^{+\bullet}$ - CH_2O - $CH_3CH_2O^\bullet$), 200 ($M^{+\bullet}$ - CH_3CH_2OCOH - $H^\bullet$), 188 ($PhC_3HNOCH_2CHOH^{+\bullet}$), 174 ($PhC_3HNOCH_2O^+$), 105 ($C_6H_5CO^+$), 77 ($C_6H_5^+$).

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88. Found: C, 61.68; H, 5.52.

3-(D-Xylofuranos-4-yl)-5-phenylisoxazole (**3**).

Compound **1** (0.26 g, 0.85 mmol) was treated with acetic acid 10%. The mixture was heated at 100 °C during 9 or 10 hours monitoring the reaction using tlc (silicagel G, toluene:ethyl acetate 1:1), until the disappearance of starting material. The reaction product was dissolved in dichloromethane, extracted with water. The resulting syrup was purified by chromatography column (silicagel G, mixtures of toluene:ethyl acetate), pure compound **3** was obtained as a syrup (0.11 g, 0.42 mmol, 49 % yield), $[\alpha]_D$ = -3.4 (c 1, methanol); ^{1}H and ^{13} C nmr see Table 1, 2 and 3; ms: m/z 264 (M + H^+), 245 ($M^{+\bullet}$ - H_2O), 227 ($M^{+\bullet}$ - 2 H_2O), 204 ($M^{+\bullet}$ - $C_2H_3O_2^\bullet$), 188 ($M^{+\bullet}$ - $C_2H_3O_3^\bullet$), 174 ($PhC_3HNOCH_2O^+$), 145 ($PhC_3H_2NO^+$), 105 ($C_6H_5CO^+$), 77 ($C_6H_5^+$).

Anal. Calcd. for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.94. Found: C, 59.01; H, 5.03.

3-[4'-(1'-Deoxy-1'-*N*-hydroxylamine-D-xylofuranosyl)]-5-phenylisoxazole (**4**).

From 3-[4-(D-xylofuranosyl)]-5-phenylisoxazole (**3**) (0.69 g, 2.63 mmoles) and using the procedure described in the literature [13], we obtained compound **4** (0.61 g, 2.18 mmoles, 83%) as a syrup; ^{1}H nmr (methanol d_4), α-anomer: δ 5.08 (d, $J_{1',2'}$ = 5.7 Hz, 1H, H-1'), 4.89 (d, $J_{4',3'}$= 4.2 Hz, 1H, H-4'), 4.17 (dd, $J_{2',1'}$= 5.8 Hz, $J_{2',3'}$= 4.9 Hz, 1H, H-2'), 3.97 (t, $J_{3',2'}$= $J_{3',4'}$= 4.5 Hz, 1H, H-3') ppm; β-anomer: δ 5.18 (d, $J_{1',2'}$ = 4.8 Hz, 1H, H-1'), 4.72 (d, $J_{4',3'}$= 1.0 Hz, 1H, H-4'), 4.01 (dd, $J_{2',1'}$= 5.0 Hz, $J_{2',3'}$= 1.5 Hz, 1H, H-2'), 3.95 (dd, $J_{3',2'}$= 1.9 Hz, $J_{3',4'}$= 1.9 Hz, 1H, H-3'), 6.59 and 6.57 (s, 2H, H-4 for both structures), 7.24-7.65 (m, 5H, aromatic protons for both structures) ppm; ^{13}C nmr (methanol d_4), α-anomer: δ 170.6 (C-5), 164.2 (C-3), 131.2, 130.0, 128.6, 126.6 (aromatic carbons), 104.3 (C-1'), 101.0 (C-4), 78.5 (C-2'), 77.7 and 75.4 (C-3' and C-4'); β-anomer: δ 170.5 (C-5), 164.4 (C-3), 131.2, 130.0, 128.6, 126.6 (aromatic carbons), 111.4 (C-1'), 101.4 (C-4), 81.6 (C-2'), 79.0 and 78.1 (C-3' and C-4'); ms: m/z 278 (M + H^+), 259 ($M^{+\bullet}$ - H_2O), 245 ($M^{+\bullet}$ - NH_2OH), 228 ($M^{+\bullet}$ - H_2O - $NHOH^\bullet$), 188 ($M^{+\bullet}$ - HCONHOH - CO), 174 ($PhC_3HNOCH_2O^+$), 145 ($PhC_3H_2NO^+$), 105 ($C_6H_5CO^+$), 77 ($C_6H_5^+$).

3-(1',2',3'-Tri-*O*-benzoyl-3'-cyano-L-xylotriitol-1'-yl)-5-phenylisoxazole (**5**).

The crude oxime **4** (0.26 g, 0.95 mmol) was dissolved in 1 mL of pyridine and 1 mL of benzoyl chloride was added in small portions. The mixture was heated in a water bath and the reaction was monitored using tlc (silicagel G, benzene:ethyl acetate 90:10), until the disappearance of starting material. The reaction product was dissolved in dichloromethane, extracted with saturated solution of sodium bicarbonate, then with hydrochloric acid 1 *N*, dried with sodium sulfate, and evaporated. The resulting syrup was purified by flash chromatography (silicagel G, mixtures of toluene:ethyl acetate), pure compound **5** was obtained as a syrup (0.16 g, 0.28 mmol, 30 % yield), $[\alpha]_D$ = +38.6° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 7.26-8.20 (aromatic protons), 6.87 (d, $J_{2',3'}$ = 5.7 Hz, 1H, H-2'), 6.60 (s, 1H, H-4), 6.32 (t, $J_{3',2'}$= 5.6 Hz, $J_{3',4'}$= 5.2 Hz, 1H, H-3'), 6.18 (d, $J_{4',3'}$= 5.3 Hz, 1H, H-4'); ^{13}C nmr: δ 171.3 (C-5), 165.1, 164.9 and 164.1 (carbonyl carbons), 160.0 (C-3), 134.4, 134.0, 130.7, 130.2, 130.1, 129.0, 128.8, 128.7, 128.5, 128.3, 127.4, 126.7, 125.9 (aromatic carbons), 114.3 (C≡N), 98.5 (C-4), 70.6 (C-2'), 66.5 (C-1'), 60.2 (C-3'); ms: m/z 572 ($M^{+\bullet}$), 467 ($M^{+\bullet}$ - $PhCO^\bullet$), 450 ($M^{+\bullet}$ - $PhCO_2H$), 412 ($M^{+\bullet}$ - $CNCHOCOPh^\bullet$), 345 ($M^{+\bullet}$ - $(PhCO)_2O$ - $H^\bullet$), 328 ($M^{+\bullet}$ - 2 $PhCO_2H$), 279 ($PhC_3HNOCH_2OCOPh^{+\bullet}$), 174 ($PhC_3HNOCH_2OCOPh^{+\bullet}$ - $PhCO^\bullet$), 122 ($PhCO_2H^{+\bullet}$), 105 ($C_6H_5CO^+$), 77 ($C_6H_5^+$), 51 ($C_4H_3^+$). HRMS Calcd. for $C_{34}H_{24}N_2O_7$: 572.1584. Found: 572.1587.

Anal. Calcd. for $C_{34}H_{24}N_2O_5$: C, 71.32; H, 4.22. Found: C, 71.19; H, 4.05.

3-(1',2',3'-Tri-*O*-benzoyl-3'-tetrazolyl-L-xylotriitol-1'-yl)-5-phenylisoxazole (**6**).

Compound **5** (0.11 g, 0.19 mmol) was dissolved in 1 mL of dimethylformamide. Then 0.14 g of ammonium chloride and 0.18 g of sodium azide were added. The mixture was heated at 40° in a water bath until all nitrile was consumed (checked by tlc), the reaction mixture was concentrated under diminished pressure. The resulting syrup was purified by flash chromatography (silicagel G, mixtures of acetone:cyclohexane), pure compound **6** was obtained as a syrup (0.07 g, 0.11 mmol, 57 % yield), $[\alpha]_D$ = +16.1° (c 1, chloroform); ^{1}H nmr (deuteriochloroform): δ 7.16-8.00 (aromatic protons), 6.99 (d, $J_{1',2'}$ = 5.1 Hz, 1H, H-1'), 6.70 (t, $J_{2',1'}$= 5.4 Hz, $J_{2',3'}$= 5.7 Hz, 1H, H-2'), 6.68 (d, $J_{3',2'}$= 5.4 Hz, 1H, H-3'), 6.61 (s, 1H, H-4); ^{13}C nmr: δ 171.0 (C-5), 165.4, 165.3 and 165.2 (carbonyl carbons), 160.4 (C-3), 155.9 (tetrazolic carbon), 133.6, 133.5, 130.4, 128.8, 128.7, 128.5, 128.3, 128.2, 127.0, 126.6, 125.8 (aromatic carbons), 98.5 (C-4), 72.4 (C-2'), 67.3 (C-3'), 66.0 (C-1'); ms: m/z 570 ($M^{+\bullet}$- N_3H - H_2), 423 ($M^{+\bullet}$ - $PhCO_2H$ - N_4H_2), 343 ($M^{+\bullet}$ - $PhCO_2H$ - N_2), 122 ($PhCO_2H^{+\bullet}$), 105 ($C_6H_5CO^+$), 77 ($C_6H_5^+$), 51 ($C_4H_3^+$).

Anal. Calcd. for $C_{12}H_{18}N_4O_5 \bullet C_4H_8O_2$: C, 49.74; H, 6.74. Found: C, 49.45; H, 6.35.

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